EXHIBIT 21

Patients With Traumatic Brain Injury
Population-Based Study Suggests Increased Risk of Stroke

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Background and Purpose—Previous studies have identified an array of morbidities following traumatic brain injury (TBI), including certain neurological disorders. However, no direct evidence has been reported on the link between TBI and stroke. This population-based study was designed to estimate the risk of stroke during a period of 5 years following a TBI, compared with individuals who did not suffer TBI during the same period.

Methods—Data were obtained from the Longitudinal Health Insurance Database 2000 (LHID 2000). A total of 23 199 patients receiving ambulatory or hospitalization care with a diagnosis of TBI were included, together with 69 597 non-TBI patients as our comparison group, matched by sex, age, and year of index use of health care. Each individual was followed for 5 years to identify subsequent occurrence of stroke. Cox proportional hazard regressions were performed for analysis.

Results—During the 3-month follow-up period, 675 strokes (2.91%) occurred in TBI patients and in 207 patients (0.30%) in the non-TBI comparison cohort. A diagnosis of TBI was independently associated with a 10.21 (95% CI, 8.71–11.96), 4.61 (95% CI, 4.16–5.11), and 2.32 (95% CI, 2.17–2.47) times greater risk of stroke during 3-month, 1-year, and 5-year follow-up, respectively, after adjusting for sociodemographic characteristics and selected comorbidities. The risk of intracerebral hemorrhage was more noticeable among patients with TBI compared with those without a TBI.

Conclusions—This is the first report showing an increased risk of stroke among individuals who have sustained a TBI. We suggest a need for more intensive medical monitoring and health education following TBI, especially during the first few months and years. **(*Stroke*. 2011;42:2733-2739.)**

Key Words: Traumatic brain injury ■ stroke ■ epidemiology

Traumatic brain injuries (TBI) are major causes of morbidity and mortality in both developing and developed countries.[1,2] Incidence rates of 235, 103, 344, and 160 per 100 000 people have been reported in Europe,[1] the United States,[3–5] Taiwan,[6] and India,[7] respectively. In the United States, a national estimate indicated that approximately 1893 in 100 000 people sustain a TBI with residual disability, impairment, or handicap as a result.[4] This is almost certainly an underestimate of the true burden of TBI.[8]

TBI has been described as a silent epidemic, because the problems or impairment following TBI may be invisible.[9] Previous studies found convincing evidence that people who survive a TBI may have consequences with persistent effects, including changes in employment, physical complaints, memory problems, neuropsychological difficulties, and family disruption.[1] Masel and DeWitt have proposed that TBI may initiate an ongoing, possibly lifelong, process that affects multiple organ systems and may cause or accelerate the progression of diseases.[10]

Chronic diseases that may be attributed to previous TBI in the literature include epilepsy,[11] gradual decline in cognitive function,[12] Alzheimer's disease,[13] Parkinson's disease,[14] hypopituitarism,[15] metabolic dysfunction,[16] and psychiatric diseases (eg, obsessive-compulsive disorder, anxiety disorder, psychotic disorders, and mood disorders).[17]

Furthermore, any damage to the brain usually causes impairment to the vascular system, which supplies blood and nutrients to the cells of the brain. A stroke, resulting from disturbance in the blood supply to the brain, is a cerebrovascular event involving loss of brain functions. It is thus rational to speculate that cerebrovascular damage in the head caused by a TBI may further trigger the occurrence of stroke, either through bleeding from the artery (hemorrhagic stroke) or through the development of a clot at the locus of injury that blocks blood flow to the brain (ischemic stroke).[18] Nevertheless, no direct evidence at all, to the best of our knowledge, has been reported regarding a link between TBI and stroke.

This nationwide, population-based study was designed to estimate the risk of stroke during a 5-year follow-up period after an ambulatory care visit or hospitalization for TBI, compared with individuals who did not suffer TBI during the

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same period. Effects were documented and analyzed from relatively short-term (3 months) to long-term (5 years).

Methods

Database

This study used data obtained from the Longitudinal Health Insurance Database 2000 (LHID 2000), which is released annually by the Taiwan National Health Research Institute, and is provided to scientists in Taiwan for research purposes. The LHID 2000 includes all the original claims data for 1 000 000 individuals randomly sampled from the year 2000 Registry of Beneficiaries (n=23.72 million) under the National Health Insurance (NHI) program. The Taiwan National Health Research Institute reports that there is no significant difference in the sex distribution between the beneficiaries selected for the LHID 2000 and all beneficiaries of the NHI program. The completeness and accuracy of the claims data of NHI research database were appropriately monitored and maintained by Taiwan's NHI Bureau, and more than 300 studies based on these data have been published in peer-reviewed journals.[19,20]

The LHID 2000 consists of de-identified secondary data released to the public for research purposes. After consulting the director of the Institutional Review Board of Taipei Medical University, this study was exempted from full review.

Study Sample

This study was a prospective case-control study. We first selected patients who had visited ambulatory care centers (including outpatient departments of hospitals or clinics) or had been hospitalized with a principal diagnosis of TBI (ICD-9-CM codes 801–804 or 850–854) between January 1, 2001 and December 31, 2003 (n=31 982). Patients' first ambulatory care visits or hospitalizations for the treatment of TBI between 2001 and 2003 were assigned as the index use of health care services. We excluded patients younger than age 18 years old (n=7 333) in order to address only the adult population. In addition, we excluded patients who had a diagnosis of acute stroke simultaneously during that admission (n=79), since TBI may mimic a first stroke in clinical practice, and vice versa. Patients who had been diagnosed with stroke (ICD-9-CM codes 430–437) before their index use of health care services were likewise excluded (n=1371). Because the Taiwan NHI program began in 1995, the LHID 2000 only allows us to trace use of medical services as far back as 1996, thus we could not rule out patients who had a diagnosis of stroke before 1996. The resulting study cohort included 23 199 TBI patients.

The comparison cohort was extracted from the remaining beneficiaries in the LHID 2000. All beneficiaries who had previously visited ambulatory care centers or been hospitalized with a diagnosis of TBI between 1996 and 2008 were excluded. Patients who were younger than age 18 years old were also excluded. We then randomly selected 69 834 beneficiaries (3 for every patient with TBI) matched with the study group in terms of sex, age (<30, 30–39, 40–49, 50–59, 60–69, and >69), and the year of index use of health care services using the SAS program Proc SurveySelect (SAS System for Windows, Version 8.2). We assigned the first ambulatory care visit occurring in the year of index health care use as their index health care use. We likewise ensured that patients selected for the comparison cohort did not have any diagnosis of stroke before their index use of health care services. Ultimately, 92 796 patients were included in this study. Each patient in this study was individually traced for 5 years from their index use of health care to distinguish patients who subsequently suffered acute stroke (ICD-9-CM codes 430–437). In Taiwan, all medical facilities capable of admitting stroke patients are equipped with computed tomography or magnetic resonance imaging scanners, which considerably increases the validity of stroke diagnosis.

Statistical Analysis

We used the SAS statistical package (SAS System for Windows, Version 8.2) to perform statistical analyses on all of the data in this study. The primary end point of this study was to find whether a patient had used ambulatory care or emergency medical services, or had undergone hospitalization for any type of acute stroke (ICD-9-CM codes 430–437). The 3-month, 1-year, or 5-year stroke-free survival rates were subsequently estimated by the Kaplan-Meier method, with the log rank test also being used to examine differences in stroke-free survival rates between cohorts. Stratified Cox proportional hazard regressions (stratified by sex, age group, and year of index health care use) were performed to compare the 3-month, 1-year, or 5-year stroke-free survival rates between 2 cohorts, after adjusting for monthly income, geographic region (Northern, Central, Eastern, and Southern Taiwan), and select comorbidities (hypertension, diabetes, coronary heart disease, heart failure, atrial fibrillation, and hyperlipidemia). Comorbidities were only counted if the condition either occurred in an inpatient setting or appeared in 2 or more ambulatory care claims coded 6 months before and after index use of health care services. We further analyzed stroke-free survival rates between cohorts by stroke and TBI subtype. The stroke subtypes are subarachnoid hemorrhage (ICD-9-CM code 430), intracerebral hemorrhage (ICD-9-CM code 431), ischemic stroke (ICD-9-CM codes 433, 434, and 435) and unspecified strokes (ICD-9-CM codes 436 and 437). We also analyzed TBI subtypes: TBI with skull bone fracture (ICD-9-CM codes 801–804) and TBI without skull bone fracture (ICD-9-CM codes 850–854).

We also censored patients who died of nonstroke causes during the 3-month, 1-year, or 5-year follow-up period (7 436 patients died over a 5-year follow-up period, including 2226 TBI patients [9.6% of TBI patients] and 5210 comparison patients [7.5% of comparison patients]). A 2-sided probability value of <0.05 was considered statistically significant for this study.

Results

Table 1 presents the distribution of demographic characteristics and comorbidities among sampled patients. Of the total of 92 796 patients, the mean age was 41.6 years (SD=18.4 years), and 53.6% were men. After matching for age and sex, patients with TBI were more likely to have hypertension ($P<0.001$), diabetes ($P<0.001$), coronary heart disease ($P<0.001$), atrial fibrillation ($P=0.001$), and heart failure ($P<0.001$) than were patients in the comparison cohort. No significant difference in hyperlipidemia ($P=0.770$) between patients with TBI and the comparison patients was found.

Table 2 displays the percentage of strokes during the 3-month, 1-year, or 5-year follow-up period after index health care use among patients with and without TBI. As compared with patients in the comparison cohort, patients with TBI had significantly higher stroke rates within the 3-month (2.91% versus 0.30%), 1-year (4.17% versus 0.96%), and 5-year (8.20% versus 3.89%) periods after index use of health care services. The log rank test suggests that patients with TBI had significantly lower 3-month, 1-year, or 5-year stroke-free survival rates compared with patients in the comparison cohort (all $P<0.001$). The Kaplan-Meier curves for strokes in patients stratified by TBI are presented in Figure. In addition, the result suggests that the average time between index use of health care services and onset of stroke was 717 days (SD=565 days) for patients who had stroke during the follow-up period (543 days and 838 days for patients with TBI and comparison patients, respectively; $P<0.001$).

Table 2 also shows the crude and adjusted hazard ratio (HR) of stroke between the cohorts. Stratified Cox proportional hazard regressions (stratified by sex, age group, and year of index health care use) shows that HRs for stroke for patients with TBI were 10.20 times as high within the

Table 1. Demographic Characteristics and Comorbid Medical Disorders for Patients in Taiwan, Stratified by the Presence or Absence of Traumatic Brain Injury, 2001–2003 (N=92 796)

	Patients With TBI (n=23 199)		Comparison Patients (n=69 597)		
Characteristic	No.	%	No.	%	*P*
Sex					1.000
Male	12 431	53.6	37 293	53.6	
Female	10 768	46.4	32 304	46.4	
Age, y					1.000
<30	8167	35.2	24 501	35.2	
30–39	3948	17.0	11 844	17.0	
40–49	3924	16.9	11 772	16.9	
50–59	2605	11.2	7815	11.2	
60–69	2005	8.7	6015	8.7	
>69	2550	11.0	7650	11.0	
Monthly income, NT$					<0.001
0	8432	36.4	26 410	38.0	
1–15840	4081	17.6	10 449	15.0	
15 841–25 000	8144	35.1	21 687	31.2	
>25 001	2542	11.0	11 051	15.9	
Geographic region					<0.001
Northern	9027	38.9	33 270	47.8	
Central	5912	25.5	16 447	23.6	
Southern	7637	32.9	18 212	26.2	
Eastern	623	2.7	1668	2.4	
Hypertension	3802	16.4	9916	14.3	<0.001
Diabetes	2037	8.8	4836	7.0	<0.001
Hyperlipidemia	1767	7.6	5342	7.7	0.770
Coronary heart disease	1808	7.8	4344	6.2	<0.001
Heart failure	550	2.4	1115	1.6	<0.001
Atrial fibrillation	99	0.4	199	0.3	0.001

US$1=NT$33.

TBI indicates traumatic brain injury; NT$, Taiwanese dollar; NT, New Taiwan.

3-month period (95% CI, 8.71–11.96; $P<0.001$), 4.61 times as high within the 1-year period (95% CI, 4.16–5.11; $P<0.001$), and 2.34 times as high within the 5-year period (95% CI, 2.20–2.50; $P<0.001$) as with patients who had not experienced TBI. Furthermore, the HR of stroke during the 3-month, 1-year, or 5-year follow-up period after index health care use for patients with TBI was 10.21 (95% CI, 8.71–11.96; $P<0.001$), 4.61 (95% CI, 4.16–5.11; $P<0.001$), and 2.32 (95% CI, 2.17–2.47; $P<0.001$), respectively, compared with non-TBI patients; this was calculated after censoring cases who died of causes unrelated to stroke during the follow-up period, and after adjusting for monthly income, patient geographic location, hypertension, diabetes, coronary heart disease, heart failure, atrial fibrillation, and hyperlipidemia.

Table 3 presents HR of stroke between cohorts according to TBI subtype. We found that 1373 cases (5.9%) and 21 826 (94.1%) of 23 199 TBI cases were TBI with skull bone fracture and TBI without skull fracture, respectively. The risk of stroke among patients with skull fracture was more pronounced than among patients without skull bone fracture. As compared with the comparison cohort, the adjusted HR of stroke during the 3-month, 1-year or 5-year follow-up period after index health care use for patients with TBI with skull fracture was 19.98 (95% CI, 14.73–27.22; $P<0.001$), 8.39 (95% CI, 7.47–10.89; $P<0.001$), and 3.54 (95% CI, 2.86–4.37; $P<0.001$), respectively.

Table 4 further shows the analysis of HR of stroke between the 2 cohorts by stroke subtype. It consistently shows that compared with non-TBI patients, patients with TBI were more likely to experience all subtypes of stroke during the 5-year follow-up period after index health care use. It is noteworthy that the adjusted HR for intracerebral hemorrhage for patients with TBI was 6.33 times as high within the 5-year period as for patients who had not experienced TBI.

Discussion

To the best of our knowledge, this is the first study to demonstrate that TBI is a potential risk factor for subsequent stroke. During a 5-year follow-up, 8.2% of TBI patients experienced stroke (1 901 patients), whereas 3.89% of non-TBI patients (2 710 patients) in the comparison cohort had strokes. After adjusting for sociodemographic characteristics, region of residence, and selected comorbidities, a diagnosis of TBI was independently associated with a 10.21-, 4.61-, and 2.32-fold increased risk of subsequent stroke during 3 months, 1 year, and 5 years of follow-up, respectively. In terms of TBI subtypes, the risk of stroke among patients with skull fracture was more pronounced than among patients without skull fracture, both compared with those in the comparison cohort. In addition, the risk of subarachnoid hemorrhage and intracerebral hemorrhage increased more considerably in patients with TBI, compared with individuals unaffected by TBI.

TBI may contribute to subsequent conditions that cause or accelerate disease.[10] Patients with TBI and their families may have to cope with TBI-induced disability, an ongoing and progressing medical condition that occurs months or even years following TBI. Previous studies have identified an array of post-traumatic morbidities, including epilepsy,[21] neurological disorders,[11] neurodegenerative diseases,[12] neuroendocrine disorders,[15] psychiatric diseases,[17] and other non-neurological disorders of sexual dysfunction[22] and metabolic dysfunction.[23] Disturbed sleep[24] and increased incidence of obstructive sleep apnea[25] have also been found in TBI patients. Stroke is the most serious and disabling neurological disorder worldwide. Our study leads the way in identifying stroke as an additional neurological problem that may arise following TBI.

The mechanism by which a TBI may influence the incidence of stroke is still vague. Yet, several possibilities could help explain the link between TBI and stroke. First, damage to the cerebrovascular system caused by a TBI might disturb blood supply to the brain and cause a stroke. Specifically,

Table 2. Crude and Adjusted Hazard Ratios of Stroke Among Sampled Patients During the 3-Month, 1-Year, and 5-Year Follow-Up Periods From Index Health Care Utilization (N=92 796)

	Total		Patients With TBI		Comparison Cohort	
Stroke Occurrence	No.	%	No.	%	No.	%
3-Mo follow-up						
Yes	882	0.95	675	2.91	207	0.30
No	91 914	99.05	22524	97.09	69390	99.70
Crude HR (95% CI)	. . .		10.20* (8.71–11.93)		1.00	
Adjusted HR (95% CI)	. . .		10.21* (8.71–11.96)		1.00	
1-Y follow-up						
Yes	1637	1.76	968	4.17	669	0.96
No	91 159	98.24	22231	95.83	68928	99.04
Crude HR (95% CI)	. . .		4.61* (4.17–5.11)		1.00	
Adjusted HR (95% CI)	. . .		4.61* (4.16–5.11)		1.00	
5-Y follow-up						
Yes	4611	4.97	1901	8.20	2710	3.89
No	88 185	95.03	21298	91.8	66887	96.11
Crude HR (95% CI)	. . .		2.34* (2.20–2.50)		1.00	
Adjusted HR (95% CI)	. . .		2.32* (2.17–2.47)		1.00	

TBI indicates traumatic brain injury; HR, hazard ratio; HR, hazard ratio; CI, confidence interval.

*$P<0.001$. Hazard ratio was calculated by using stratified Cox proportional regression (stratified on sex age group and the year of index healthcare use) with cases censored if individuals died from non-stroke causes during the 3-month, 1-year, or 5-year follow-up period. Adjustments were made for patient's monthly income, geographic region, and select comorbidities (hypertension diabetes coronary heart disease heart failure atrial fibrillation and hyperlipidemia).

lack of blood flow caused by blockage (ischemic stroke) may stem from clot formation at the site of injury and other parts of the head, or may result from the loosening of clots from an atherosclerotic blood vessel with the sudden impact of TBI. Conversely, leakage of blood (hemorrhagic stroke) could be caused in part by bleeding from an artery after a TBI.[18,26] Our study indeed identified risks of hemorrhagic stroke that increase considerably more among patients with TBI. Patients with blunt trauma may further suffer from blunt cerebrovascular injuries, a potentially devastating injury with subsequent stroke rates up to 50%.[27] Moreover, increase in intracranial pressure and blood pressure commonly observed among patients with TBI may lead to subsequent risk of stroke.[28,29] Finally, antipsychotic drugs used to treat patients with TBI might contribute to greater stroke incidence.[30] Patients with TBI may display aggressive behavior or other psychiatric symptoms that demand prescription medication. However, cumulative evidence has revealed that antipsychotic drugs increase the risk of stroke, especially the atypical drugs.[31,32]

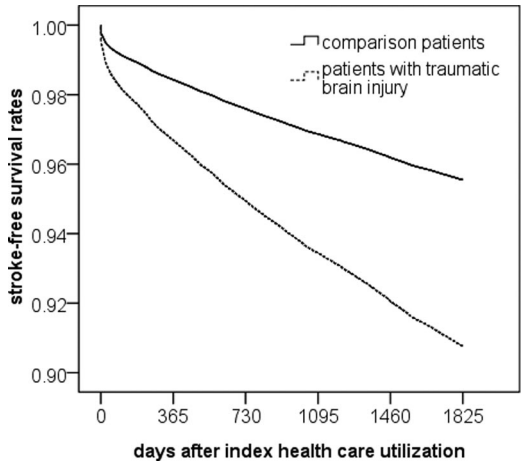

Figure. Stroke-free survival rates for patients with traumatic brain injury and comparison cohort in Taiwan, 2001 to 2003.

We also found that in addition to increased risk of stroke, patients with TBI were slightly more likely to be diagnosed with traditional stroke risk factors within 6 months before or after the TBI incident, compared with unaffected individuals. These stroke risk factors include hypertension, diabetes mellitus, cardiovascular disease (coronary heart disease, cardiac failure), and atrial fibrillation.[29,33] It is possible that patients with TBI receive more medical care afterward and thus, additional diseases are more likely to be identified. In contrast, TBI might be related to certain types of morbidity (eg, hypertension[34]). Accordingly, select comorbid diseases were considered and adjusted for in the regression analyses in our study to evaluate better the association between TBI and stroke.

TBI and stroke are both issues of momentous concern, because large numbers of people sustain such insults and require extensive rehabilitation in the acute and chronic stages of recovery. Our findings thus have important clinical implications in the management of patients with TBI. More intensive medical monitoring, support, and intervention are

Table 3. Crude and Adjusted Hazard Ratios of Stroke Among Sampled Patients During 3-Month, 1-Year, and 5-Year Follow-Up Periods From Index Health Care Utilization According to TBI Subtype (N=92 796)

	Comparison Cohort		Patients With TBI With Skull Fracture		Patients With TBI Without Skull Fracture	
Stroke Occurrence	No.	%	No.	%	No.	%
3-Mo follow-up						
Yes	207	0.30	58	4.22	617	2.83
No	69390	99.70	1315	95.78	21209	97.17
Crude HR (95% CI)	1.00		19.44* (14.35–26.34)		9.76* (8.32–11.44)	
Adjusted HR (95% CI)	1.00		19.98* (14.73–27.22)		9.75* (8.31–11.45)	
1-Y follow-up						
Yes	669	0.96	73	5.32	895	4.10
No	68928	99.04	1300	94.68	20931	95.90
Crude HR (95% CI)	1.00		8.12* (6.27–10.51)		4.45* (4.02–4.94)	
Adjusted HR (95% CI)	1.00		8.39* (7.47–10.89)		4.44* (4.00–4.93)	
5-Y follow-up						
Yes	2710	3.89	115	8.38	1786	8.18
No	66887	96.11	1258	91.62	20040	91.82
Crude HR (95% CI)	1.00		3.47* (2.81–4.28)		2.29* (2.15–2.45)	
Adjusted HR (95% CI)	1.00		3.54* (2.86–4.37)		2.26* (2.12–2.42)	

TBI indicates traumatic brain injury; HR, hazard ratio; CI, confidence interval.

*$P<0.001$. Hazard ratio was calculated by using stratified Cox proportional regression (stratified on sex age group and the year of index health care use) with cases censored if individuals died from non-stroke causes during the 3-month, 1-year, or 5-year follow-up period. Adjustments were made for patient's monthly income, geographic region, and select comorbidities (hypertension diabetes coronary heart disease heart failure atrial fibrillation and hyperlipidemia).

required following a TBI, especially during the first few months or years, as the risk of stroke decreases gradually after TBI, from 3 months post-trauma (almost 10 times the normal risk) to 5 years (about twice the risk). In an acute stroke situation, prompt recognition of symptoms and timely medical attention within the first hours of onset are essential. Favorable outcomes were identified among patients who began appropriate treatment (eg, tissue-type plasminogen activator for the treatment of acute ischemic stroke) within 3 hours of stroke symptom onset.[35] However, lack of awareness or recognition of initial stroke symptoms caused delayed arrival at medical centers, with only a few patients receiving prompt medical care.[36,37] Thus, there is need for health education and intervention to increase family awareness of factors involved in stroke and early signs/symptoms of stroke in patients with TBIs.[38] The treating medical team should also be aware of the need to provide early neuroimaging examination (such as magnetic resonance imaging) for suspected stroke patients, particularly those with a history of TBI.

There are 2 main strengths of this study. First, our findings are the results from a nationwide, population-based, case-cohort study, which met the criteria for sound epidemiological study to investigate properly the association between TBI and stroke. Second, selection and nonresponse biases may have been minimized by the comprehensive coverage of the NHI system and the large sample size.

However, 4 caveats deserve attention. First, the NHI database only includes patients who sought treatment for TBI and stroke. Nevertheless, both TBI and stroke, especially moderate-to-severe cases, are medical conditions that require prompt medical treatment and management. The NHI system has contracts with an extensive network of health care institutions distributed well throughout the country. Easy access to medical services (emergency/outpatient/hospitalization) and very low out-of-pocket payments decrease the possibility that TBI and stroke cases, particularly ones of moderate-to-severe degree, would be left unattended. Second, issues on potential lost to follow-up should be of concern. Nevertheless, the NHI program is a nationwide system covering about 99% of Taiwan's population. Internal migration of the insured should not be a problem in our study. A small proportion of the insured may move out of the country during the follow-up period; however many return for health care services because of Taiwan's low copayment and medical expenses.

Third, the NHI claims data set does not include important parameters indicating clinical severity and imaging information on TBI and stroke. Lack of external causes of TBI (eg, motor vehicle crashes, falls, violence) restricted us from additional subgroup analysis. Finally, important variables that might affect the risk of stroke were unavailable in our administrative claims data set, including body mass index, diet, physical activity level, smoking, and alcohol consumption.

Conclusions

This is the first evidence-based finding to suggest an increased risk of stroke among individuals who have suffered a

Table 4. Crude and Adjusted Hazard Ratios of Stroke by Stroke Subtype Among Sampled Patients During 5-Year Follow-Up From Index Health Care Utilization

	Total n=92 796		Patients With TBI n=23 199		Comparison Cohort n=69 597	
Stroke Occurrence	No.	%	No.	%	No.	%
Subarachnoid hemorrhage						
Yes	155	0.17	94	0.41	61	0.09
Crude HR (95% CI)			4.83* (3.82–7.17)		1.00	
Adjusted HR (95% CI)			4.89* (3.81–7.19)		1.00	
Intra-cerebral hemorrhage						
Yes	664	0.72	457	1.92	207	0.30
Crude HR (95% CI)			6.28* (5.58–7.77)		1.00	
Adjusted HR (95% CI)			6.33* (5.60–7.83)		1.00	
Ischemic stroke						
Yes	2617	2.82	857	3.69	1760	2.53
Crude HR (95% CI)			1.46* (1.34–1.60)		1.00	
Adjusted HR (95% CI)			1.43* (1.31–1.56)		1.00	
Unspecified stroke						
Yes	1175	1.27	493	2.13	682	0.98
Crude HR (95% CI)			2.23* (2.02–2.47)		1.00	
Adjusted HR (95% CI)			2.21* (1.99–2.44)		1.00	

TBI indicates traumatic brain injury; HR, hazard ratio; CI, confidence interval.

*$P<0.001$. Hazard ratio was calculated by using stratified Cox proportional regression (stratified on sex age group and the year of index health care use) with cases censored if individuals died from non-stroke causes during the 5-year follow-up period. Adjustments were made for patient's monthly income, geographic region, and select comorbidities (hypertension diabetes coronary heart disease heart failure atrial fibrillation and hyperlipidemia).

TBI. A coordinated and systematic approach should be adopted to prevent patients with TBI from subsequent stroke and to optimize outcomes. Future studies are needed to elucidate the mechanisms by which TBI is associated with stroke. To provide additional insight into the link between TBI and stroke, effects of severity, subtypes, and external causes of TBI on subsequent risk of stroke or type of stroke should be examined.

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Disclosures

None.

References

1. Tagliaferri F, Compagnone C, Korsic M, Servadei F, Kraus J. A systematic review of brain injury epidemiology in Europe. *Acta Neurochir*. 148:255–268, 2006; discussion 68.
2. Alaranta H, Koskinen S, Leppanen L, Palomaki H. Nationwide epidemiology of hospitalized patients with first-time traumatic brain injury with special reference to prevention. *Wiener medizinische Wochenschrift (1946)*. 2000;150:444–448.
3. Kraus J, McArthur D. Brain and spinal cord injury. In: Nelson M, Tanner C, eds. Neuroepidemiology: from principles to practice. New York, NY: Oxford University Press; 2004.
4. Langlois JA, Rutland-Brown W, Thomas KE. Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations, and Deaths. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2004.
5. Torner J, Choi S, Barnes T. Epidemiology of head injuries. In: Marion D, ed. Traumatic brain injury. New York, NY: Thieme; 1999.
6. Chiu WT, Yeh KH, Li YC, Gan YH, Chen HY, Hung CC. Traumatic brain injury registry in Taiwan. *Neurological Res*. 1997;19:261–264.
7. Gururaj G, Sastry KV, Chandramouli B, Subbakrishna D. Neurotrauma registry in the NIMHANS.: National Institute of Mental Health & Neurosciences, Bangalore, India; 2004.
8. Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. *J Head Trauma Rehabil*. 2006;21:375–378.
9. Langlois JA, Marr A, Mitchko J, Johnson RL. Tracking the silent epidemic and educating the public: CDC's traumatic brain injury-associated activities under the TBI Act of 1996 and the Children's Health Act of 2000. *J Head Trauma Rehabil*. 2005;20:196–204.
10. Masel BE, DeWitt DS. Traumatic brain injury: a disease process, not an event. *J Neurotrauma*. 2010;27:1529–1540.
11. Yasseen B, Colantonio A, Ratcliff G. Prescription medication use in persons many years following traumatic brain injury. *Brain Inj*. 2008;22:752–757.
12. Till C, Colella B, Verwegen J, Green RE. Postrecovery cognitive decline in adults with traumatic brain injury. *Arch Phys Med Rehabil*. 2008;89:S25–S34.
13. Jellinger KA, Paulus W, Wrocklage C, Litvan I. Traumatic brain injury as a risk factor for Alzheimer disease. Comparison of two retrospective autopsy cohorts with evaluation of ApoE genotype. *BMC Neurol*. 2001;18:1:3.
14. Bower JH, Maraganore DM, Peterson BJ, McDonnell SK, Ahlskog JE, Rocca WA. Head trauma preceding PD: a case-control study. *Neurology*. 2003;60:1610–1615.
15. Schneider HJ, Kreitschmann-Andermahr I, Ghigo E, Stalla GK, Agha A. Hypothalamopituitary dysfunction following traumatic brain injury and aneurysmal subarachnoid hemorrhage: a systematic review. *JAMA*. 2007;298:1429–1438.

16. Borsheim E, Bui QU, Wolfe RR. Plasma amino acid concentrations during late rehabilitation in patients with traumatic brain injury. *Arch Phys Med Rehabil*. 2007;88:234–238.
17. Fleminger S. Long-term psychiatric disorders after traumatic brain injury. *Eur J Anaesthesiol Suppl*. 2008;42:123–130.
18. Vital M. Traumatic Brain Injury: Hope Through Research.: National Institute of Neurological Disorders and Stroke; National Institutes of Health. NIH Publication No. 02–158. From http://www.ninds.nih.gov/disorders/tbi/detail_tbi.htm; 2002.
19. Chen YC, Yeh HY, Wu JC, Haschler I, Chen TJ, Wetter T. Taiwan's National Health Insurance Database: administrative health care database as study object in biblometrics. *Scientometrics*. 2011;86:365–380.
20. Kang JH, Chung SD, Xirasagar S, Jaw FS, Lin HC. Increased risk of stroke in the year after a hip fracture: a population-based follow-up study. *Stroke*. 2011;42:336–341.
21. Annegers JF, Hauser WA, Coan SP, Rocca WA. A population-based study of seizures after traumatic brain injuries. *N Engl J Med*. 1998;338:20–24.
22. Zasler ND, Katz DI, Zafonte RD. Brain Injury Medicine: Principles and Practice. New York, NY: Demos Medical Publishing; 2006.
23. Aquilani R, Viglio S, Iadarola P, Guarnaschelli C, Arrigoni N, Fugazza G, et al. Peripheral plasma amino acid abnormalities in rehabilitation patients with severe brain injury. *Arch Phys Med Rehabil*. 2000;81:176–181.
24. Masel BE, Scheibel RS, Kimbark T, Kuna ST. Excessive daytime sleepiness in adults with brain injuries. *Arch Phys Med Rehabil*. 2001;82:1526–1532.
25. Castriotta RJ, Wilde MC, Lai JM, Atanasov S, Masel BE, Kuna ST. Prevalence and consequences of sleep disorders in traumatic brain injury. *J Clin Sleep Med*. 2007;3:349–356.
26. Sims NR, Muyderman H. Mitochondria, oxidative metabolism and cell death in stroke. *Biochim Biophys Acta*. 2010;1802:80–91.
27. Stein DM, Boswell S, Sliker CW, Lui FY, Scalea TM. Blunt cerebrovascular injuries: does treatment always matter? *J Trauma*. 66:132–143, 2009; discussion 43–44.
28. Graham DI, Gennareli TA. Pathology of brain damage after head injury. In: Cooper P, Golfinos G, eds. Head Injury. IV Ed. New York, NY: McGraw-Hill Professional; 2000.
29. Romero JR, Morris J, Pikula A. Stroke prevention: modifying risk factors. *Ther Adv Cardiovasc Dis*. 2008;2:287–303.
30. Glenn MB. Sudden cardiac death and stroke with the use of antipsychotic medications: implications for clinicians treating individuals with traumatic brain injury. *J Head Trauma Rehabil*. 2010;25:68–70.
31. Gill SS, Rochon PA, Herrmann N, Lee PE, Sykora K, Gunraj N, et al. Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study. *BMJ*. 2005;330:445.
32. Herrmann N, Mamdani M, Lanctot KL. Atypical antipsychotics and risk of cerebrovascular accidents. *Am J Psychiatry*. 2004;161:1113–1115.
33. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke*. 1991;22:312–318.
34. Labi ML, Horn LJ. Hypertension in traumatic brain injury. *Brain Inj*. 1990;4:365–370.
35. National Institute of Neurological Disorders and Stroke rtPA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:1581–1587.
36. Reed SD, Cramer SC, Blough DK, Meyer K, Jarvik JG. Treatment with tissue plasminogen activator and inpatient mortality rates for patients with ischemic stroke treated in community hospitals. *Stroke*. 2001;32:1832–1840.
37. Tan TY, Chang KC, Liou CW. Factors delaying hospital arrival after acute stroke in southern Taiwan. *Changgeng Yi Xue Za Zhi*. 2002;25:458–463.
38. Kim YS, Park SS, Bae HJ, Cho AH, Cho YJ, Han MK, et al. Stroke awareness decreases prehospital delay after acute ischemic stroke in Korea. *BMC Neurol*. 2011;11:2.